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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/736,252	12/15/2003	David Finkelstein	3567.1	4665
22886	7590	02/10/2006	EXAMINER	
AFFYMETRIX, INC ATTN: CHIEF IP COUNSEL, LEGAL DEPT. 3420 CENTRAL EXPRESSWAY SANTA CLARA, CA 95051			ZHOU, SHUBO	
			ART UNIT	PAPER NUMBER
			1631	

DATE MAILED: 02/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/736,252	Applicant(s) DAVID, FINKELSTEIN	
	Examiner Shubo (Joe) Zhou	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
 4a) Of the above claim(s) 1-10, 17 and 18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 11-16, 19 and 20 is/are rejected.
- 7) ☒ Claim(s) 11-16, 19 and 20 is/are objected to.
- 8) ☒ Claim(s) 1-20 are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 15 December 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Restriction/Election Requirement

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-10, drawn to a method for analyzing microarray analysis quality using principal component analysis (PCA), classified in class 702, subclass 19.

II. Claims 11-20, drawn to a method for analyzing microarray analysis quality using analysis of variance (ANOVA), classified in class 702, subclass 19.

2. The inventions are distinct, each from the other because of the following reasons.

Inventions of groups I and II are directed to related but distinct processes. The related inventions are distinct if the inventions as claimed are mutually exclusive; are not obvious variants; and are either not capable of use together or can have a materially different design, mode of operation, function, or effect. See MPEP § 806.05(j). In the instant case, the methods of the different groups are related because they are used to analyze microarray analysis quality metrics, but the methods are mutually exclusive, not obvious variants and have different modes of actions, functions and effects. Group I involves using PCA, and group II involves using ANOVA. It is clear from the instant specification that the two methods are distinct method of statistical analysis involving distinct parameters, steps and produce different results. “[P]rincipal component analysis (PCA) is used to analyze the variability of the quality parameters (metrics) for experimental conditions. Principle component analysis (PCA) allows the representation of the effects of all parameters in a few vectors. Liner transformation of the quality metrics may be

employed when the quality metrics are not normally distributed.” When microarray analysis quality is evaluated using analysis of variance (ANOVA), “outliers by replication would then be counted and summed for each array then the quality metrics for a set of arrays would be collected and correlated to the expression outlier sum. Multivariate models can be tested and the best predictive subset where all independent variables were significant and the adjusted r squared maximized can be selected ... The ANOVA model would then provide diagnostic information to best discern which quality issue most influenced signal.” ... “A benefit of and [sic]ANOVA model is that it provides information of how well a transcript follows the model, in other words the biological effect, but it will also provide information on data that do not follow the model. Outliers for each probe set were derived from residuals from the ANOVA. See pages 3-4 of the specification. Therefore, the inventions of groups I and II are distinct.

Because these inventions are distinct for the reasons given above, they have acquired a separate status in the art. The search required for the groups are not co-extensive because each group requires a different non-patent literature search due to their comprising different method steps and producing different results. Thus, there would be serious search burden if both groups were examiner together. Therefore, the restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Species Election Applied to both Groups I and II

3. This application contains claims directed to the following patentably distinct species of

the claimed invention:

(A) a method for analyzing microarray analysis quality data involving discrete quality metrics, such as claims 4 and 14, and

(B) a method for analyzing microarray analysis quality data involving cumulative quality metrics, such as claims 7 and 17.

The specification states that discrete measures give an indication of the progress of one step in the process. For example, Bio B reports the efficiency of the labeling and the hybridization, but does not tell us anything about the RNA quality. Cumulative measures on the other hand report the success of all previous steps in the process. For example, a percent-present measure in the normal range would indicate success of all previous steps in the process: the RNA must have been of good quality, the hybridization and labeling must have worked well and the software must have been applied properly. See page 3. The methods involving discrete metrics and cumulative metrics are distinct because they involves different parameters, factors and steps and produce different results.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, (A) or (B), for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1-3,9-10,11-13, and 19-20 are generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after

the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

5. During a telephone conversation with Wei Zhou on 1/11/06, a provisional election, without traverse, was made to prosecute the invention of group II and species (A). Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-10 and 17-18 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention or species.

Claims 11-16 and 19-20 are under consideration.

Specification

6. The specification is objected to because of the following:

Trademarks are used in this application, such as GENECHIP on page 8. Trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The following phrase appeared on page 4, line 3 and page 28, line 15 is confusing: “A benefit of and the ANOVA model” It seems that the word “and” before “the ANOVA” should be deleted.

Some of the capitalized letters appeared in the specification (underlined herein), such as “All Signal values were log transformed ...” on page 30, line 1, and “Quality Control” on page 32, line 4, are confusing. It is not clear why they should be capitalized.

The specification on page 5, line 6, refers to Figures 9A and 9B (note the plural “Figures”), however, the drawings filed on 12/15/03 only contains a Figure 9 which contains parts A, B and C. Language such as Figure 9 part A, part B, part C should be used. If separate figures such as Figure 9A and Figure 9B are desired, they should be so separately filed.

Certain misspellings are noticed in the specification, such as “principle component analysis” on page 27, line 17. It appears that “principal component analysis” should be recited.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 11-16 and 19-20 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims are drawn to a process of performing ANOVA of microarray quality metrics data and analyzing outliers.

MPEP 2106 states in various paragraphs regarding patent eligibility:

"The claimed invention as a whole must accomplish a practical application. That is, it must produce a "useful, concrete and tangible result." State Street, 149 F.3d at 1373, 47 USPQ2d at 1601-02. The purpose of this requirement is to limit patent protection to inventions that possess a certain level of "real world" value, as opposed to subject matter that represents nothing more than an idea or concept, or is simply a starting point for future investigation or research (Brenner v. Manson, 383 U.S. 519, 528-36, 148 USPQ 689, 693-96); In re Ziegler, 992, F.2d 1197, 1200-03, 26 USPQ2d 1600, 1603-06 (Fed. Cir. 1993)). Accordingly, a complete disclosure should contain some indication of the practical application for the claimed invention, i.e., why the applicant believes the claimed invention is useful.

"If the "acts" of a claimed process manipulate only numbers, abstract concepts or ideas, or signals representing any of the foregoing, the acts are not being applied to appropriate subject matter. Schrader, 22 F.3d at 294-95, 30 USPQ2d at 1458-59. Thus, a process consisting solely of mathematical operations, i.e., converting one set of numbers into another set of numbers, does not manipulate appropriate subject matter and thus cannot constitute a statutory process. In practical terms, claims define nonstatutory processes if they:

- consist solely of mathematical operations without some claimed practical application (i.e., executing a "mathematical algorithm"); or*
- simply manipulate abstract ideas, e.g., a bid (Schrader, 22 F.3d at 293-94, 30 USPQ2d at 1458-59) or a bubble hierarchy (Warmerdam, 33 F.3d at 1360, 31 USPQ2d at 1759), without some claimed practical application."*

In the instant case, the claimed invention as a whole (e.g. claim 11) is merely a process of manipulation of data without producing a practical application, i.e. concrete, tangible and useful result. The process consists solely of mathematical operations by calculating variances of the data through ANOVA and analyzing the outliers derived from residuals of the ANOVA analysis. The process does not produce a concrete, tangible and useful result because it does not provide a clear result for the step of "analyzing outliers." While outliers are referred to in the specification in paragraphs 9, 10, 23, 82-84, and 136 (paragraph numbers are from the published version of the application (20040180365), neither the claims nor the specification provide practical utilities for analyzing the outliers in direct relationship with analyzing microarray analysis quality, which is recited in the preamble of the claims, or any other practical applications.

Claim Rejections-35 USC § 112

9. The following is a quotation of the **second** paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 13-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase “wherein principal analysis comprises ...” recited in claim 13 lacks clear antecedent basis. Claim 13 depends from claim 12, which, in turn, depends from claim 11. Neither claim 12 nor claim 11 recites or requires principal analysis. The metes and bounds of the claimed invention in claim 13 are thus not clear.

Claims 14-16 are rejected as being dependent from claim 13 and thus also containing the indefinite limitation.

Clarification of the metes and bounds of the claims is requested.

Claim Rejections-35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 11-14 and 16 are rejected under 35 U.S.C. § 102(b) as being anticipated by Finkelstein et al. (CAMDA 2000 Conference, Critical Assessment of Microarray Data Analysis).

The claims are drawn to a method for analyzing microarray analysis quality comprising performing an ANOVA of microarray quality metrics data and analyzing outliers, wherein the outliers are derived from residuals from the ANOVA. In light of the indefiniteness of the claims set forth above, the art is being applied to the best interpretation of the claims as written.

Note that ANOVA is an acronym for “analysis of variance.” See specification, page 3, line 17. Quality metrics are defined as quality parameters in the specification. See page 3, line 12. Accordingly, parameters that affect the microarray quality, such as spatial effect (spot locations) and RNA quality, are interpreted as quality metrics.

The cited art by Finkelstein et al. is found as a presentation in CAMDA conference 2000 held on 12/19/2000. See page 2 of 3 of the printout of “CAMDA 2000 Conference Agenda” from the website <http://www.camda.duke.edu/camda00/agenda/>. The cited article is found from a hyperlink referred to as “presentation” in “CAMDA 2000 Conference Submitted Abstracts” with the URL <http://www.camda.duke.edu/camda00/papers/>. The cited paper is printed from the link <http://www.camda.duke.edu/camda00/papers/days/papers/finkelstein/presentation>. The printed paper bears a date “1/25/2001” at the bottom of each page.

Finkelstein et al. disclose a method for analyzing microarray analysis quality data including such parameters as spatial bias. The method comprises performing ANOVA on the microarray data, and analyzing outliers derived from residuals of the ANOVA analysis. The simple ANOVA used by Finkelstein et al. yields an F-test and r-squared valued. See page 1 of 7, Abstract, the 3rd paragraph, and page 2 of 7, “Spatial Methods.”

With regard to claim 12, Finkelstein et al. disclose that the microarray analysis is for analyzing the yeast gene expression analysis by cross-hybridization. See Abstract.

With regard to claim 13, Finkelstein et al. disclose that the analysis comprises log transformation of the microarray data. See Abstract, the 3rd paragraph. As to the limitation “non-normally distributed quality metrics,” it is inherent that the data to be log transformed by

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Finkelstein et al. are non-normally distributed. It has been somewhat controversial as to whether or not the expression levels for different genes are normally distributed. Chen et al., after applying several statistical tests to a large set of microarray data, conclude that the “hypothesis on normality of gene expression levels should be rejected beyond all reasonable doubt.” See Chen et al., page 6, “Conclusions.”

With regard to claim 14, which recites “discrete quality metrics,” the specification states that “discrete measures give an indication of the progress of one step in the process. For example, Bio B reports the efficiency of the labeling and the hybridization, but does not tell us anything about the RNA quality.” See page 3, lines 1-3. Since the spatial factor/spatial bias analyzed by Finkelstein et al. only reports the effect of the locations of probes on the array, but does not report anything about the RNA quality, etc., it is interpreted as being a discrete quality metrics.

With regard to claim 16, parameter of background is considered and analyzed by Finkelstein et al. See page 2 of 7, last paragraph, and legend of Figure 1 on page 3 of 7.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

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2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Finkelstein et al. (CAMDA 2000 Conference, Critical Assessment of Microarray Data Analysis), as applied to claims 11-14 and 16 above, and further in view of Duggan et al. (Nature Genetics Supplement, Vol. 21, pages 10-64, 1999).

Claim 15 is drawn to a method for analyzing microarray analysis quality comprising performing an ANOVA of microarray quality metrics data and analyzing outliers, wherein the outliers are derived from residuals from the ANOVA, and wherein the quality metrics comprise RNA quality metrics.

As applied to claims 11-14 and 16 above, Finkelstein et al. disclose a method for analyzing microarray analysis quality data including such parameters as spatial bias. The method comprises performing ANOVA on the microarray data, and analyzing outliers derived from residuals of the ANOVA analysis.

Finkelstein et al. suggest analyzing different parameters by stating that “empirical evidence and observations validated by statistical tests have indicated that several distinct types of consistent measurement error can alter the interpretation of cDNA microarray data. Whenever possible models of error are derived during quality assessment and applied during data analysis.” See Abstract, first paragraph.

However, Finkelstein et al. do not explicitly teach analyzing RNA quality metrics.

Duggan et al. disclose expression profiling using cDNA microarray. Duggan et al. analyze parameters affecting the quality of microarray analysis and state that “the purity of RNA is a critical factor in hybridization performance, particularly when using fluorescence, as cellular

proteins, lipid and carbohydrate can mediate significantly non-specific binding of fluorescently labeled cDNAs to slide surfaces.” see page 12, left column.

Thus, a person of ordinary skill in the art would have been motivated by Finkelstein et al. to analyze more parameters/metrics in addition to spatial bias because they suggest that several distinct types of consistent measurement error can alter the interpretation of cDNA microarray data, and whenever possible models of error are derived during quality assessment and applied during data analysis, and would have been motivated by Duggan et al. to modify the method by Finkelstein et al. to also analyze the RNA quality metrics in addition to spatial bias because Duggan et al. suggest the quality of RNA is a critical factor in hybridization performance. Therefore, analyzing RNA quality metrics by performing ANOVA and analyzing outliers would have been obvious to a person of ordinary skill in the art at the time the invention was made.

15. Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Finkelstein et al. (CAMDA 2000 Conference, Critical Assessment of Microarray Data Analysis), as applied to claims 11-14 and 16 above, and further in view of Hacia, J.G. (Nature Genetics Supplement, Vol. 21, 1999).

The claims are drawn to a method for analyzing microarray analysis quality comprising performing an ANOVA of microarray quality metrics data and analyzing outliers, wherein the outliers are derived from residuals from the ANOVA, and wherein the microarray analysis is genotyping analysis (claim 19) or resequencing analysis (claim 20).

As applied to claims 11-14 and 16 above, Finkelstein et al. disclose a method for analyzing microarray analysis quality data including such parameters as spatial bias. The method comprises performing ANOVA on the microarray data, and analyzing outliers derived from

residuals of the ANOVA analysis, wherein the microarray analysis is gene expression analysis and cross homology analysis.

Finkelstein et al. suggest wide area application for microarrays by stating that “Best practice of microarray data analysis is directly ties to the application of the data. If the arrays are to be used as rapid screening tools then sophisticated normalization and analysis may not be necessary. If, however, the object of the experiment is to model subtle biological patterns ... much more complex analysis is required.” See page 7 of 7.

However, Finkelstein et al. do not explicitly teach using microarray for genotyping analysis and re-sequencing analysis.

Hacia teaches using oligonucleotide microrarrays for resequencing and mutational analysis including genotyping analysis. See page 42, right column, page 43 and 45. Hacia states that among the greatest strengths of array-based mutational analysis is the ability to detect specific sequence changes of interest. Once specific hybridization patterns or ‘signatures’ of large numbers of mutant alleles of interest are known, it will be possible to search for those signatures in many different samples simultaneously. See page 45, right column. Further, Hacia disclose that microarray has been used for diverse applications. See page 42, left column.

A person of ordinary skill in the art would have been motivated by Finkelstein et al. and Hacia to use microarray for applications more than gene expression analysis, and would have been motivated by Hacia to modify the method by Finkelstein et al. to use oligonucleotide arrays for resequencing and genotyping to take array’s advantage of allowing sequencing all variants and determining all alleles (signatures) of a gene involving in a particular disease and searching for the signatures in multiple samples simultaneously. Therefore, analyzing quality data of microarray analysis for resequencing and genotyping by performing ANOVA and analyzing outliers would have been obvious to a person of ordinary skill in the art at the time the invention was made.

Claim Objections

16. Claims 11-16 and 19-20 are objected to because of the following informalities:

The use of capitalized letter “P” in the “performing” step and the capital letter “A” in the “analyzing” step recited in claim 11 is confusing. The MPEP, section 608.01(m) [R-3], states:

“While there is no set statutory form for claims, the present Office practice is to insist that each claim must be the object of a sentence starting with “I (or we) claim,” “The invention claimed is” (or the equivalent) Each claim begins with a capital letter and ends with a period.”

Claims 12-16 and 19-20 are objected to as being dependent from claim 11.

Grammatical errors are present in claims 14-16, which recite “wherein the quality metrics comprises....” Given the plural form of the word “metrics” (meaning parameters in the instant application, see specification, page 3, line 12), it follows that “wherein the quality metrics comprise” should be recited.

Appropriate correction is required.

Conclusion

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shubo (Joe) Zhou, whose telephone number is 571-272-0724. The examiner can normally be reached Monday-Friday from 8 A.M. to 4 P.M. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel,

Ph.D., can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent Analyst Tina Plunkett whose phone number is (571) 272-0549.

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Shubo (Joe) Zhou, Ph.D.



Patent Examiner